Quantitative imaging in radiation oncology

Research impact and utilisation summary

1 Societal impact

In this thesis, we analysed and proposed solutions to some major issues currently limiting the application of AI to medical imaging in radiation oncology. These issues are strongly impacting the possibility to translate research prototypes as decision support systems in the clinic. Decision support systems bring a benefit not only to clinicians, but also to patients. The ongoing challenge for radiation oncology is to provide patients with the best possible treatment. The treatment strategy must be as good as possible, boosting curative intent, while decreasing the risk of radiation-induced side effects and disease relapse. When achieved, cancer patients will live longer and better. Many of our treatment decisions are based on the evidence arising from randomized clinical trials. While we recognize the importance of clinical trials, we also highlight how the evidence from clinical trials should be expanded with a "real life" evidence. It is a well-known problem that strict requirements for trials' accrual can lead to results that only apply to a small population, which might not be representative of the variety of patients walking into the clinic every day. In this thesis, I present how AI applied to medical imaging is key to improve patient care in the near future. I discuss how medical images are a source of unique patient-centred data, which can reveal insights about our patients. I show and propose AI-driven techniques for automated image analysis and biomarker discovery that can lead to the development of robust decision support systems (DSSs). These DSSs redefine and augment our clinicians' prior knowledge because they consider unique information based on the patient-level. Biomarkers are derived from medical images, which contain fingerprints of patients' anatomy and tumours. By proposing a robust methodology for automated medical image analysis (i.e., *radiomics*), this thesis is contributing in the near future to speed up the translation of image-derived biomarkers in the clinic with the societal impact of supporting better decisions for the treatment of cancer patients. While the work has been mainly devoted to lung and head neck cancers, it is scalable to many other anatomical sites and even diseases not necessarily related to cancer, since medical images are the most frequent type of data acquired in a clinic.

2 Economic Impact

In the last years, radiation oncology has faced an "explosion" of treatment options. Besides conventional radiation therapy and surgery, the recent advances in biology have opened the path to therapies that interact with our immune systems (immunotherapy) to suppress cancer cells or by targeting specific molecular profiles of tumours (molecular or targeted therapies). Even for more traditional therapies like surgery, hardware advances such as robotics is improving our surgeons' abilities to be more precise and therefore, reduce post-surgery complications. For treatment with radiation, alternatives to conformal radiotherapy are for example represented by proton/ion therapy, which can improve radiation delivered to the targets, while reducing damage to surrounding healthy tissues. Doctors are struggling to pick the best option since sometimes there is not enough evidence that on a patient-level one treatment should be preferred over another. An additional problem also comes into the game: many of these techniques are still very expensive. This problem connects to the optimization of the health care system. In the Netherlands, healthcare is regulated by health insurance providers. These providers will be willing to reimburse the above-mentioned treatment options, but only after showing them the efficacy of these treatments on a large scale. Re-defining the evaluation of the best treatment options for a patient is therefore the key to improve cost-effectiveness. Using image derived biomarkers as an additional tool to support clinicians in finding the best treatment option, as stated in this thesis, will, in the long term, boost cost-effectiveness. Using medical imaging to objectively quantify treatment response, will reduce the risk of providing a treatment which could have been stated to be beneficial at the time of planning, but could become harmful with a strong impact not only of patients' health, but also on unnecessary costs. Even if it was out of scope for this thesis to perform a cost-effective analysis, the developments presented in this work will have an economic impact on the long term. Finally, the approaches presented in this thesis are directly applied to standard of care medical imaging modalities (e.g., PET/CT, MRI). Scans that are acquired anyway in the radiotherapy workflow, therefore no additional investment of money is required to gain more information useful for care decisions.

3 Cultural Impact

This thesis tackles some of the problems related to the introduction of AI to improve our ability to make better-informed decisions. When it comes to the application of AI for the automation of time-consuming tasks, we are more willing to accept that an autonomous artificially intelligent "entity" can replace us. However, when it comes to be supported by AI in our decisions, we are more reluctant to accept this shift in paradigm. I believe that two of the major causes behind these discrepancies are: A) the poor performance of AI-based prognostic and predictive models in radiotherapy, and B) the false myth that AI applications in radiotherapy are meant to replace the users, requiring only negligible human interaction. With regard to the former, this thesis has been devoted to investigating the issues that are causing the degrade of radiomics-based models' performances when validated on multiple datasets. I have proposed methods that can support more transparent and robust developments of image-derived biomarkers and shown how cautions are required when using AI, or more specifically ML and DL, to draw conclusions. With regard to the latter, I have shown that even in the presence of fully or semi-automated image analysis and modelling pipelines, a human interaction is required to verify the correctness of assumptions, as well as the benchmarking of newly discovered biomarkers with traditionally accepted prognostic of predictive factors in radiation oncology. Finally, in the last chapter of the thesis, I have discussed solutions to improve the acceptance of AI in the clinic, with a dedicated focus on the role of multiple stakeholders. This thesis is proposing the paradigm to re-shift human-centricity when using AI. This will have a strong cultural impact, and, in my opinion, it will boost the acceptance of AI.

4 Technological impact

This thesis did not per se developed a new hardware technology. Nevertheless, it contains two promising potential technological products. The first product is an image-analysis framework which consists of multiple processing pipelines, image harmonization, extraction of image derived biomarkers, quality assurance of these biomarkers and modelling. This pipeline can easily be inserted in the clinical workflow or within the clinical workstations. Potential users are scanner manufactures, as well as companies developing clinical workstations or AI solutions. Second, in the third part of the thesis, a framework based on a distributed learning solution for radiomics was presented. This data infrastructure has the impact to alleviate the effort required to collect and process data on a centralized repository. The technology is not limited to traditional machine learning algorithms, but it can be extended to distributed deep learning. Overall, this technology has the impact that even smaller centres, with availability of fewer data compared for example to large institutions, will be able to perform large scale experiments, with the benefit of training and validating algorithms on data with an order of magnitude larger than the sample size simply available in the single clinic. Finally, this thesis introduced the concept of FAIR withing medical imaging studies. The re-think of radiomic studies as FAIR-compliant experiments enriches the reproducibility of such experiments and enables inter-operability of multiple radiomic computational packages.